

APPENDIX  
New Claims 13-39

13. A method for the prophylactic treatment of a subject at risk of developing a cardiovascular disorder which comprises treating the subject with a therapeutically effective amount of a cyclooxygenase-2 inhibitor, or a pharmaceutically-acceptable salt thereof in combination with an agent selected from the group consisting of (1) a lipid lowering drug, (2) an anti-oxidant, (3) a IIb/IIIa antagonist, (4) an aldosterone inhibitor, (5) an AII antagonist, (6) a  $\beta$ -blocker, (7) aspirin, (8) a loop diuretic and (9) an ace inhibitor.

14. The prophylactic treatment method of claim 13 wherein said subject is treated with said cyclooxygenase-2 inhibitor, or said pharmaceutically acceptable salt thereof, in combination with said lipid lowering drug.

15. The prophylactic treatment method of claim 14 wherein said lipid lowering drug is selected from the group consisting of (1) an IBAT inhibitor, (2) a fibrate, (3) niacin, (4) a statin, (5) a CETP inhibitor and (6) a bile acid sequestrant.

16. The prophylactic treatment method of claim 15 wherein said lipid lowering drug is a statin.

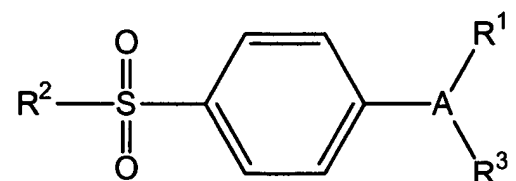
17. The method of claim 16 wherein the cardiovascular disorder is an inflammation-related cardiovascular disorder.

18. The method of claim 16 wherein the cardiovascular disorder is selected from coronary artery disease, aneurysm, arteriosclerosis, atherosclerosis, myocardial infarction, embolism, stroke, thrombosis, angina, coronary plaque inflammation, bacterial induced inflammation, viral induced inflammation and inflammation associated with surgical procedures.

19. The method of claim 18 wherein the cardiovascular disorder is atherosclerosis.

20. The method of claim 19 wherein the cyclooxygenase-2 inhibitor, or said pharmaceutically acceptable salt thereof, has a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50.

21. The method of claim 19 wherein the cyclooxygenase-2 inhibitor has the formula



where A is selected from oxazolyl, isoxazolyl, furyl, thienyl, dihydrofuryl, pyrrolyl, pyrazolyl, thiazolyl, imidazolyl, isothiazolyl, benzofuryl, cyclopentenyl, cyclopentadienyl, phenyl and pyridyl;

R¹ is selected from pyridyl optionally substituted at a substitutable position with one or more methyl radicals and phenyl optionally substituted at a substitutable position with one or more radicals selected from methyl, ethyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, fluoromethyl, difluoromethyl, trifluoromethyl, cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl, hydroxy, hydroxymethyl, trifluoromethoxy, amino, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, phenylamino, methoxymethyl, methylsulfinyl, fluoro, chloro, bromo, methoxy, ethoxy, propoxy, n-butoxy, pentoxy and methylthio;

R² is selected from methyl and amino

R³ is selected from hydrido, oxo, cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl, carboxypropyl, carboxymethyl, carboxyethyl, cyanomethyl, fluoro, chloro, bromo, methyl, ethyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, cyclohexyl, phenyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl, pyrazinyl, hydroxymethyl, hydroxypropyl, benzyl, formyl, phenylcarbonyl, methoxymethyl, furylmethoxymethyl, aminocarbonyl, N-methylaminocarbonyl, N,N-dimethylaminocarbonyl, N,N-dimethylamino, N-ethylamino,

N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, aminomethyl, N,N-dimethylaminomethyl, N-methyl-N-ethylaminomethyl, benzyloxy and phenoxy.

22. The method of claim 19 wherein the cyclooxygenase-2 inhibitor is selected from MK-966 (Merck & Co.); L-752,860 (Merck & Co.); L-783,003 (Merck & Co.); T-614 (Toyama); D-1367 (Chiroscience); L-748,731 (Merck & Co.); L-745,337 (Merck & Co.); 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide; 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide; 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide; 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine; 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine; 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide; 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide; 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide; [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide; 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide; and 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl]-4-oxazolyl]benzenesulfonamide.

23. The method of claim 22 wherein the cyclooxygenase-2 inhibitor is MK-966 (Merck & Co.).

24. A method for preventing atherosclerosis in a subject at risk of developing atherosclerosis which comprises treating the subject with a therapeutically effective amount of a cyclooxygenase-2 inhibitor, or a pharmaceutically-acceptable salt thereof in combination with an agent selected from the group consisting of (1) a lipid lowering drug, (2) an anti-oxidant, (3) a IIb/IIIa antagonist, (4) an aldosterone inhibitor, (5) an AII antagonist, (6) a  $\beta$ -blocker, (7) aspirin, (8) a loop diuretic and (9) an ace inhibitor.

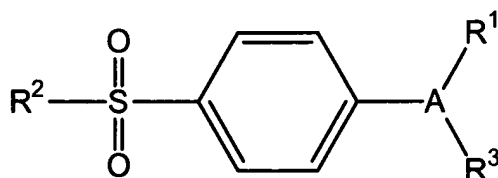
25. The method of claim 24 wherein said subject is treated with said cyclooxygenase-2 inhibitor, or said pharmaceutically acceptable salt thereof, in combination with said lipid lowering drug.

26. The method of claim 25 wherein said lipid lowering drug is selected from the group consisting of (1) an IBAT inhibitor, (2) a fibrate, (3) niacin, (4) a statin, (5) a CETP inhibitor and (6) a bile acid sequestrant.

27. The method of claim 26 wherein said lipid lowering drug is a statin.

28. The method of claim 27 wherein the cyclooxygenase-2 inhibitor, or said pharmaceutically acceptable salt thereof, has a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50.

29. The method of claim 27 wherein the cyclooxygenase-2 inhibitor has the formula



where A is selected from oxazolyl, isoxazolyl, furyl, thienyl, dihydrofuryl, pyrrolyl, pyrazolyl, thiazolyl, imidazolyl, isothiazolyl, benzofuryl, cyclopentenyl, cyclopentadienyl, phenyl and pyridyl;

R<sup>1</sup> is selected from pyridyl optionally substituted at a substitutable position with one or more methyl radicals and phenyl optionally substituted at a substitutable position with one or more radicals selected from methyl, ethyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, fluoromethyl, difluoromethyl, trifluoromethyl, cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl, hydroxy, hydroxymethyl, trifluoromethoxy, amino, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, phenylamino, methoxymethyl, methylsulfinyl, fluoro, chloro, bromo, methoxy, ethoxy, propoxy, n-butoxy, pentoxy and methylthio;

R<sup>2</sup> is selected from methyl and amino

R<sup>3</sup> is selected from hydrido, oxo, cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl, carboxypropyl, carboxymethyl, carboxyethyl, cyanomethyl, fluoro, chloro, bromo, methyl, ethyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl,

difluoromethyl, trifluoromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, cyclohexyl, phenyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl, pyrazinyl, hydroxymethyl, hydroxypropyl, benzyl, formyl, phenylcarbonyl, methoxymethyl, furylmethoxymethyl, aminocarbonyl, N-methylaminocarbonyl, N,N-dimethylaminocarbonyl, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, aminomethyl, N,N-dimethylaminomethyl, N-methyl-N-ethylaminomethyl, benzyloxy and phenyloxy.

30. The method of claim 27 wherein the cyclooxygenase-2 inhibitor is selected from MK-966 (Merck & Co.); L-752,860 (Merck & Co.); L-783003 (Merck & Co.); T-614 (Toyama); D-1367 (Chiroscience); L-748,731 (Merck & Co.); L-745,337 (Merck & Co.); 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide; 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide; 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide; 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine; 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine; 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide; 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide; 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide; [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide; 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide; and 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl]-4-oxazolyl]benzenesulfonamide.

31. The method of claim 30 wherein the cyclooxygenase-2 inhibitor is MK-966 (Merck & Co.).

32. A pharmaceutical composition comprising, in a single formulation, a combination of a therapeutically effective amount of a cyclooxygenase-2 inhibitor, or a pharmaceutically-acceptable salt thereof and a therapeutically effective amount of an agent selected from the group consisting of (1) a lipid lowering drug, (2) an anti-oxidant, (3) a IIb/IIIa antagonist, (4) an aldosterone inhibitor, (5) an AII antagonist, (6) a  $\beta$ -blocker, (7) aspirin, (8) a loop diuretic and (9) an ace inhibitor.

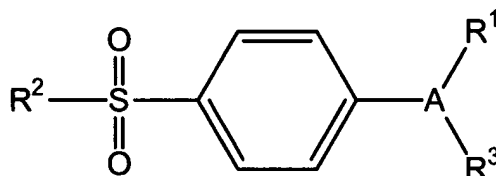
33. The composition of claim 32 comprising the combination of said cyclooxygenase-2 inhibitor, or said pharmaceutically acceptable salt thereof, and said lipid lowering drug.

34. The composition of claim 33 wherein said lipid lowering drug is selected from the group consisting of (1) an IBAT inhibitor, (2) a fibrate, (3) niacin, (4) a statin, (5) a CETP inhibitor and (6) a bile acid sequestrant.

35. The composition of claim 34 wherein said lipid lowering drug is a statin.

36. The composition of claim 35 wherein the cyclooxygenase-2 inhibitor, or said pharmaceutically acceptable salt thereof, has a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50.

37. The composition of claim 35 wherein the cyclooxygenase-2 inhibitor has the formula



where A is selected from oxazolyl, isoxazolyl, furyl, thienyl, dihydrofuryl, pyrrolyl, pyrazolyl, thiazolyl, imidazolyl, isothiazolyl, benzofuryl, cyclopentenyl, cyclopentadienyl, phenyl and pyridyl;

R¹ is selected from pyridyl optionally substituted at a substitutable position with one or more methyl radicals and phenyl optionally substituted at a substitutable position with one or more radicals selected from methyl, ethyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, fluoromethyl, difluoromethyl, trifluoromethyl, cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl, hydroxy, hydroxymethyl, trifluoromethoxy, amino, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-

methyl-N-ethylamino, phenylamino, methoxymethyl, methylsulfinyl, fluoro, chloro, bromo, methoxy, ethoxy, propoxy, n-butoxy, pentoxy and methylthio;

R<sup>2</sup> is selected from methyl and amino

R<sup>3</sup> is selected from hydrido, oxo, cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl, carboxypropyl, carboxymethyl, carboxyethyl, cyanomethyl, fluoro, chloro, bromo, methyl, ethyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, cyclohexyl, phenyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl, pyrazinyl, hydroxymethyl, hydroxypropyl, benzyl, formyl, phenylcarbonyl, methoxymethyl, furylmethoxymethyl, aminocarbonyl, N-methylaminocarbonyl, N,N-dimethylaminocarbonyl, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, aminomethyl, N,N-dimethylaminomethyl, N-methyl-N-ethylaminomethyl, benzyloxy and phenyloxy.

38. The composition of claim 35 wherein the cyclooxygenase-2 inhibitor is selected from MK-966 (Merck & Co.); L-752,860 (Merck & Co.); L-783,003 (Merck & Co.); T-614 (Toyama); D-1367 (Chiroscience); L-748,731 (Merck & Co.); L-745,337 (Merck & Co.); 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide; 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide; 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide; 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine; 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine; 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide; 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide; 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide; [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide; 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide; and 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl]-4-oxazolyl]benzenesulfonamide.

39. The composition of claim 38 wherein the cyclooxygenase-2 inhibitor is MK-966 (Merck & Co.).